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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,912	06/28/2001	Y. Tom Tang	30266/37260A	4685

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,912	TANG ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-65,74 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-65,74 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 17 March 2003 (Paper No. 11) has been entered in full. Claims 62 and 64-65 are amended and claims 74-75 are added. Claims 1-61 and 66-73 are cancelled.

Election/Restrictions

Applicant's election of Group N, drawn to a method of supporting proliferation or survival of a stem cell or germ cell in Paper No. 11 (17 March 2003) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election with traverse of the nucleotide sequence of SEQ ID NO: 12 and the amino acid sequence of SEQ ID NO: 13 in Paper No. 11 (17 March 2003) is acknowledged. The traversal is on the ground(s) that the amino acid sequence of SEQ ID NOs: 34 is 99.6% identical to the elected sequence of SEQ ID NO: 13. Applicant also argues that the murine ortholog is 86.4% identical to the amino acid sequence of SEQ ID NO: 34. After examination of the PTO sequence database results for SEQ ID NO: 13, the Examiner has found Applicant's arguments persuasive. The Examiner found SEQ ID NO: 34 to be 99.3% similar to the elected SEQ ID NO: 13 and SEQ ID NO: 32 was found to be 86.4% similar to the elected SEQ ID NO: 13. Therefore, SEQ ID NOs: 32 and 34 are rejoined to SEQ ID NO: 13.

The requirement is still deemed proper and is therefore made FINAL.

Claims 62-65 and 74-75 are under consideration in the instant application.

Priority

1. The proper priority cannot be completely determined because the first paragraph of the specification and the declaration are inconsistent. For example, the declaration does not claim priority under 35 U.S.C. § 120 to 09/757/562 (1/9/2001), 09/543,774 (4/5/2000), or 09/496,914 (2/3/2000), which are mentioned in the first line of the specification. If Applicant intends to claim priority to these applications, a new oath or declaration or application data sheet in compliance with 37 CFR 1.67(a) identifying these applications by application number and filing date is required. See MPEP §§ 602.01 and 602.02. Otherwise, these applications must be deleted from the first line of the specification.

Specification

1. The disclosure is objected to because of the following informalities:

1a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a continuation of U.S. Application No. 09/543, 774, filed April 5, 2000, now Abandoned, which in turn is a continuation-in-part of U.S. Application No. 09/496,914, filed February 3, 2000, now Abandoned" should be entered.

1b. Patent applications are referenced throughout the disclosure (pg 12, line 7, for example). The status of the applications must be updated.

1c. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see pg 165, line 18). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

1d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF PROMOTING STEM CELL PROLIFERATION OR SURVIVAL BY CONTACTING THE CELL WITH A NOVEL STEM CELL FACTOR-LIKE POLYPEPTIDE".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 62-65 and 74-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the claims are directed to a method of supporting proliferation or survival of a stem cell or germ cell comprising contacting said cell with an amount of a polypeptide having an amino acid sequence at least 85% identical to SEQ ID NO: 13 or the mature protein coding portion thereof, wherein said amount is effective to maintain survival of or promote proliferation of said cell. The claims also recite that the polypeptide comprises the amino acid sequences of either SEQ ID NO: 13, SEQ ID NO: 32, or SEQ ID NO: 34.

(i) The specification teaches that $1 * 10^4$ mouse stem cells are co-cultured with $1 *10^4$ stem cell growth factor-like polynucleotide-transduced stromal cells or vector-transduced stromal cells in serum free media. The specification discloses that on day 7, IL-3 and IL-6 are added and cultures monitored daily (pg 168, lines 5-15, Example 6). However, it is not clear from the

results listed in the specification which growth factors actually induced an increase in the proliferation of mouse stem cells (e.g., stem cell growth-factor like polynucleotide-transduced stoma cells, IL-3, IL-6, or a combination of two or more). For example, the specification does not teach the cell numbers until Day 15, wherein IL-3 and IL-6 have already been added to the cultures. There is no indication of the relative cell numbers before the addition of the two other growth factors. Additionally, this particular assay is only measuring cell proliferation. There is no guidance in the specification that this assay measured cell survival or differentiation. For example, there is no indication that the growth factors or the stem cell growth factor-like polynucleotide transduced stoma cell were removed from the media and the cells counted daily.

The specification also discloses an assay wherein $CD34^+$ hematopoietic stem cells are purified, plated, and purified stem cell growth factor-like protein and other hematopoietic cytokines are added to the cultures. The growth and differentiation of stem cells are examined 5 days after culture (pg 168-170, Example 7). Again, it is not clear from the results listed in the specification as to whether or not the stem cell growth factor-like protein promoted $CD34^+$ stem cell proliferation. For instance, the results of Experiments 1-6 (as interpreted by the legend at the top of pg 169) indicate that stem cell growth factor-like protein *alone* did not promote growth or differentiation and caused the loss of viability of the stem cells. Only in experiments with IL-3 and kit ligand/ flt-3 ligand was there a sign of growth and /or differentiation of stem cells. Furthermore, there is little guidance in the specification teaching how much growth was or was not observed in the various experiments of Example 7. The specification only shows a (+) for a positive result and a (-) for a negative result. The skilled artisan would not be able to interpret the data from these experiments or determine if there was a significant difference between the

control cells and growth-factor-added cells. Also, this particular assay is only measuring cell proliferation. There is no guidance in the specification that this assay measured cell survival or differentiation. Furthermore, although the DNA of stem cell growth factor-like protein was isolated from a stromal cell line (pg 42, lines 16-20) among other cell types (pg 164, pg 177-180), there is no guidance in the specification as to whether or not any type of stem cell or germ cell expresses the receptor for stem cell growth factor-like protein. If the cells do not express the respective receptor, the stem cell growth factor-like protein will have little or no effect upon cell growth or survival.

(ii) It is noted that the claims of the instant application are also broad enough wherein they encompass not only supporting proliferation or survival of a stem or germ cell *in vitro*, but also supporting proliferation or survival of a stem or germ cell *in vivo*. Overall, undue experimentation would be required of the skilled artisan to promote or maintain the proliferation or survival of all possible stem and germ cells (including primordial germ cell, germ line stem cells, embryonic stem cell, hematopoietic stem cells, hematopoietic progenitor cells, pluripotent cells, or totipotent cells) by contacting the cells with a polypeptide having an amino acid sequence of SEQ ID NO: 13, 32, or 34. There is little guidance in the specification or working example that indicate the stem cell growth factor-like polypeptide of SEQ ID NOs: 13, 32, and 34 is able to support or maintain cell proliferation or survival *in vitro* or *in vivo*. Undue experimentation would also be required of the skilled artisan to determine the optimal dosage, duration, and route of administration of the stem cell growth factor-like polypeptide if administered to cells *in vivo*.

(iii) Furthermore, regarding the recitation of "an amino acid sequence at least 85% identical to SEQ ID NO: 13", the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is

dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to support the proliferation or survival of all possible stem and germ cells *in vitro* and *in vivo* by contacting the cells with the polypeptide of amino acid sequence SEQ ID NO: 13, 32, or 34; to determine the quantity of stem cell growth factor-like protein to be administered *in vivo*, the most effective administration route, and the duration of the treatment; and to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the unpredictability of the effects of the stem cell growth factor-like protein *in vitro* and *in vivo,* undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant is encouraged to submit any pre- or post-filing date references or evidence in the form of a declaration under 37 C.F.R. 1.132 to support the specification.

4. Claim 62 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 62 is directed to a method of supporting proliferation or survival of a stem cell or germ cell comprising contacting said cell with an amount of a polypeptide having an amino acid sequence at least 85% identical to SEQ ID NO: 13 or the mature protein coding portion thereof, wherein said amount is effective to maintain survival of or promote proliferation of said cell. The specification teaches that the term "variant" refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions (pg 29, lines 25-27). The specification also discloses that the term "substantially equivalent" or "substantially similar" can refer to both nucleotide and amino acid sequences, for example a mutant sequence that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences (pg 30, lines 26-30). The specification also teaches that a substantially equivalent sequence varies from one of those listed therein by no more than about 35% (pg 30, lines 30-33). However, the specification does not teach functional or structural characteristics of the all possible derivatives of SEQ ID NO: 13 in the context of a cell or organism. The description of essentially two polynucleotide species (SEQ ID NO: 12 and 31) and two polypeptide species (SEQ ID NO: 13 and 34) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments with at least 85% sequence identity to the novel stem cell growth factor-like polypeptide comprising SEQ ID NO: 13.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO: 13 or the mature protein coding portion thereof, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 62-65 and 74-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The term "supporting" in claims 62-65 and 74-75 is a relative term which renders the claims indefinite. The term "supporting" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the term "supporting" encompasses. For example, does it mean "promoting", "maintaining", "decreasing", etc?

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
June 4, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER